PP2A Inhibition Is a Common Event in Colorectal Cancer and Its Restoration Using FTY720 Shows Promising Therapeutic Potential

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Abstract
Protein phosphatase 2A (PP2A) is a tumor suppressor that regulates many signaling pathways crucial for cell transformation. In fact, decreased activity of PP2A has been reported as a recurrent alteration in many types of cancer. Here, we show that PP2A is frequently inactivated in patients with colorectal cancer, indicating that PP2A represents a potential therapeutic target for this disease. We identified overexpression of the endogenous PP2A inhibitors SET and CIP2A, and downregulation of regulatory PP2A such as PPP2R2A and PPP2R5E, as contributing mechanisms to PP2A inhibition in colorectal cancer. Moreover, we observed that its restoration using FTY720 impairs proliferation and clonogenic potential of colorectal cancer cells, induces caspase-dependent apoptosis, and affects AKT and extracellular signal-regulated kinase-1/2 activation status. Interestingly, treatment with FTY720 showed an additive effect with 5-fluorouracil, SN-38, and oxaliplatin, drugs used in standard chemotherapy in patients with colorectal cancer. These results suggest that PP2A activity is commonly decreased in colorectal cancer cells, and that the use of PP2A activators, such as FTY720, might represent a potential novel therapeutic strategy in colorectal cancer.

Introduction
Colorectal cancer is a high prevalent neoplasia characterized by a progressive accumulation of genetic and epigenetic abnormalities that lead to cancer progression. Protein phosphatase 2A (PP2A) is a tumor suppressor that regulates many signaling pathways (1–3), and its loss of function has been associated with cell transformation (4–5). PP2A is not a single entity but a heterotrimeric complex consisting of a scaffold PP2A-A subunit, a catalytic PP2A-C subunit, and a regulatory PP2A-B subunit that determines both the specific substrate and the localization of the holoenzyme. Two isoforms have been described for PP2A-A and PP2A-C, and at least 26 isoforms for PP2A-B (6–7). Therefore, PP2A can form a high number of different complexes that interact with many different substrates (5).

It has been reported that transformed cells use different mechanisms to inhibit PP2A, including alterations in any of the PP2A subunits, and also the overexpression of specific endogenous inhibitors (4, 8–9). Despite PP2A has been described as a novel therapeutic target in several tumor models (10–12), the importance and potential value of PP2A as a druggable tumor suppressor in colorectal cancer remains mostly underexplored. Interestingly, there are some evidences that would suggest a relevant role of PP2A deregulation in colorectal cancer development. Alterations affecting PPP2R1B have been reported in colorectal cancer, impairing the interaction between PP2A-B and PP2A-C therefore inactivating PP2A (13–16). Furthermore, the tumor suppressor activity of PP2A seems to modulate the sensitivity of colorectal cancer cells to different treatments such as rapamycin (17), sphingodienes (18), or antiangiogenesis therapies (19). Therefore, we hypothesized that PP2A would be deregulated and could represent a novel targeted therapeutic strategy in colorectal cancer.

In this study, we show that PP2A activity is reduced in colorectal cancer, and overexpression of the endogenous PP2A inhibitors, SET or CIP2A, was identified as possible mechanisms of PP2A inhibition in colorectal cancer. Interestingly, FTY720 treatment increased PP2A activity,
affecting proliferation and clonogenic potential of colorectal cancer cells. In addition, FTY720-induced PP2A activation led to increased apoptosis and changes in the phosphorylation status of AKT and extracellular signal-regulated kinase (ERK)-1/2. Of importance, our data provide strong evidences that PP2A activation could be a promising therapeutic target in combination with drugs used in standard chemotherapy, such as 5-fluorouracil (5-FU), SN-38, or oxaliplatin (LOHP).

Materials and Methods

Cell cultures

The human colorectal cancer cell lines RKO (ATCC CRL-2577), SW480 (ATCC CCL-228), WiDr (ATCC CCL-218), DLD-1 (ATCC CCL-221), HT-29 (ATCC HTB-38), LoVo (ATCC CCL-229), and SW620 (ATCC CCL-227) were purchased from American Type Culture Collection (ATCC) and were not cultured for more than 2 months. No authenticity was done by the authors. Cell lines were maintained in RPMI-1640 (Invitrogen) following manufacturer’s indications, clarified (12,000 × g, 15 minutes, 4°C), denatured, and subjected to SDS-PAGE and Western blot analysis. Antibodies used in Western blot analysis included mouse monoclonal anti-PP2A (clone 1D6, Upstate Inc.), rabbit polyclonal anti-PP2A (FL-309; Santa Cruz Biotechnology), rabbit monoclonal anti-PP2AR307 (Epi-tech), rabbit monoclonal anti-pERK1/2Thr202/Tyr204 (Santa Cruz Biotechnology), rabbit polyclonal anti-PP2R2A (Abcam), goat polyclonal anti-PPP2R5E (Novus Biologicals), rabbit polyclonal anti-CIP2A, and mouse monoclonal anti-β-actin (Sigma). Proteins were detected with the appropriate secondary antibodies conjugated to alkaline phosphatase (Sigma) by chemiluminescence using Tropix CSPD and Tropix Nitro Block II (Applied Biosystems).

Proliferation assay and cell viability

Cell proliferation was measured in triplicate wells by MTS assay in 96-well plates using the CellTiter 96 AQeous One Solution Cell Proliferation Assay (Promega), following the manufacturer’s indications.

PP2A phosphatase activity assays

PP2A assays were performed with cell lysates (50 μg) using a PP2A immunoprecipitation phosphatase assay kit (Millipore) as previously described (20).

Analysis of caspase activation

Quantification of caspase-3/7 activities in untreated or FTY720-treated colorectal cancer cells were carried out using the caspase Glo-3/7 assay kit (Promega Corp.). Briefly, 5 × 103 cells were plated in a white-walled 96-well plate, and the Z-DEVD reagent, the luminogenic caspase-3/7 substrate containing a tetrapeptide Asp-Glu-Val-Asp, was added with a 1:1 ratio of reagent to sample. After 90 minutes at room temperature, the substrate cleavage by activated caspase-3 and -7, and the intensity of a luminescent signal were measured by a FLUOstar OPTIMA luminometer (BMG Labtech). Differences in caspase-3/7 activity in FTY720-treated cells compared with untreated cells are expressed as fold-change in luminescence.

Cloning assay

Ex vivo models

Tissue slices, which were not needed for diagnostic purposes, from primary colorectal tumors larger than 1.5 cm of maximum diameter and normal adjacent colon mucosa were obtained from surgical specimens in patients newly diagnosed for adenocarcinoma. The samples were processed in sterile conditions immediately
after surgical resection. Two slices (2 cm³) for tumor and normal mucosa were used for the present study. One of the tumor and mucosa slides (designated as control samples) were put into culture medium, and another additional tumor and mucosa slices (designated as treated samples) were put on the same culture medium plus FTY720 at 10 μmol/L. Incubation was performed in 24-well plates at 37°C in a constant atmosphere of 5% CO2 for 24 hours. At 24 hours, the specimens were fixed in 10% neutral-buffered formalin for 16 hours at room temperature and embedded in paraffin under vacuum conditions. These specimens were assayed for molecular markers as described in the immunohistochemical (IHC) section.

**Immunohistochemistry**

Tissue sections (3 μm) were placed on plus charged glass slides. After deparaffinization in xylene and graded alcohols, heat antigen retrieval was performed in pH 9 EDTA-based buffer (Dako). Endogenous peroxidase was blocked by 0.03% hydrogen peroxide for 5 minutes. Slides were incubated with primary antibodies for 60 minutes at room temperature, followed of appropriate anti-Immunglobulin horseradish peroxidase-conjugated polymer (Flex+, Dako). Sections were visualized with 3,3′-diaminobenzidine as a chromogen. All stainings were performed in a Dako Autostainer. Sections incubated with nonimmunized serum were used as negative controls.

**Results**

**Reduced PP2A activity and SET deregulation are common events in colorectal cancer**

To evaluate the importance of PP2A in colorectal cancer, we analyzed PP2A activation status in a series of 21 patients diagnosed of colorectal cancer. Patient characteristics are indicated in Supplementary Table S1. Interestingly, we observed a significant reduction of PP2A activity in 18 out of the 21 samples analyzed (Fig. 1A and Supplementary Fig. S1 and Supplementary Table S2). Because the 1D6 antibody against PP2A has been previously reported to recognize the demethylated fraction of PP2A (21–22), we performed these experiments with a second antibody against full-length PP2A (FL-309), and similar results were observed in all cases except for P4 who was
positive for PP2A inhibition only with the FL-309 antibody (Supplementary Figs. S2 and S3). To investigate the possible causes of PP2A inhibition, we sequenced PPP2R1B in the 21 patients with colorectal cancer. Information about the primers used for amplifying PPP2R1B cDNA segments is indicated in the Supplementary Table S3. Two silent heterozygous alterations were found: GAC (Asp) to GAT (Asp) at codon 391 in the patient 12 (P12), and TAT (Tyr) to TAC (Tyr) at codon 72 in patient 14 (P14; Supplementary Fig. S4). However, no missense mutations were identified in our cohort. In addition, we analyzed by Western blot analysis the expression of the PP2A endogenous inhibitor SET in these patients with colorectal cancer. We found SET overexpressed in 13 out the 21 samples analyzed (Fig. 1B and Supplementary Table S2). Taken together, these results would indicate that PP2A inactivation is a common event in colorectal cancer and that deregulation of the endogenous PP2A inhibitor SET would be a key contributing mechanism to PP2A inactivation in colorectal cancer.

**CIP2A is frequently overexpressed and correlates with c-MYC levels in colorectal cancer**

The fact that some of the patients included in our series showed reduced PP2A activity without displaying SET deregulation prompted us to study the presence of alternative mechanisms to inhibit PP2A in colorectal cancer. We studied the levels of CIP2A, another endogenous PP2A inhibitor recently reported as deregulated in colorectal cancer (23). Interestingly, we found CIP2A overexpressed in 15 out of 21 cases analyzed (Fig. 2 and Supplementary Table S2). CIP2A acts inhibiting PP2A-mediated c-MYC dephosphorylation and proteolytic degradation (24). Furthermore, CIP2A has been proposed as a key c-Myc regulator in colorectal cancer (25) and, in concordance with this point, we observed a good correlation between CIP2A and c-MYC levels in our series (Fig. 2). Therefore, these observations would suggest that CIP2A overexpression is another contributing mechanism to inhibit PP2A in colorectal cancer. To further investigate other possible mechanisms of PP2A inhibition in colorectal cancer, we analyzed by Western blot analysis, the expression of PPP2R2A and PPP2R5E. Interestingly, we found PPP2R2A downregulated in nine out of the 21 patients with colorectal cancer, and PPP2R5E downregulation in three out of 21 cases (Supplementary Table S2 and Supplementary Fig. S5). These observations would suggest that downregulation of regulatory PP2A subunits such as PPP2R2A and PPP2R5E could be involved in the PP2A inhibition observed in colorectal cancer.

**PP2A activation by FTY720 reduces cell viability in colorectal cancer cells**

We next performed functional analyses in a series of seven colorectal cancer cell lines to clarify the biologic relevance of PP2A deregulation in colorectal cancer. We first analyzed the PP2A status and the expression levels of SET and CIP2A in our panel of colorectal cancer cell lines observing that all of them showed PP2A inhibition together with overexpression of both SET and CIP2A in comparison with normal controls (Supplementary Fig. S6). To assess whether increased PP2A activity affects cell proliferation of colorectal cancer cells, RKO and LoVo cell lines were treated with the PP2A activator FTY720 or vehicle (DMSO). Phosphatase assays to quantify PP2A activity levels confirmed that FTY720 treatment leads to PP2A activation (Fig. 3A and Supplementary Fig. S7). In addition, we pretreated RKO and LoVo cells with the PP2A inhibitor okadaic acid for 90 minutes, followed by incubation with FTY720 or vehicle for 24 hours. FTY720-induced PP2A activity in RKO and LoVo cells was inhibited by okadaic acid (Fig. 3A). Western blot analysis showed that similar levels of PP2Ac protein were immunoprecipitated in the PP2A phosphatase assays (Fig. 3B), suggesting that differences observed in PP2A activity are not due to changes in PP2Ac expression levels. We next analyzed the effect of PP2A activation on cell growth using MTS assay. We observed a decreased proliferation in FTY720-treated RKO and LoVo cells compared with vehicle-treated cells (Fig. 3C). Similar results were obtained with the SW480, HT-29, and DLD-1 cell lines (Supplementary Fig. S8). In addition, we observed that the impaired proliferation induced by FTY720 was partially rescued by the treatment with okadaic acid used at a concentration that inhibits PP2A but no other phosphatases (Fig. 3C and Supplementary Fig. S8; ref. 26). Moreover, the images obtained after treatment with FTY720, using an optical microscope, were in concordance with the
MTS results (Supplementary Fig. S9). Altogether, these results show that PP2A activation by FTY720 treatment induces toxicity in colorectal cancer cells.

FTY720 leads to an impaired clonogenic potential of colorectal cancer cells that is dependent on PP2A activation

To further confirm the importance of FTY720-modulating colorectal cancer cell proliferation, we determined the effects on colony-forming ability of FTY720 treatment in colorectal cancer cells. Interestingly, FTY720-treated RKO and LoVo cells formed a markedly reduced number of colonies than controls (Fig. 4). In concordance with the results obtained in the proliferation assays, we observed that the impaired clonogenic ability induced by FTY720 was partially rescued by the treatment with okadaic acid, indicating that this effect is at least partially promoted by PP2A activation. Similar results were also obtained with the HT-29 and DLD-1 cell lines (Supplementary Fig. S10). These results would suggest a potential therapeutic value for FTY720 treatment through PP2A activation in colorectal cancer cells.

FTY720 induces apoptosis in colorectal cancer cells

To further investigate the biologic effect of the FTY720-induced PP2A activation in colorectal cancer, RKO cells were treated with FTY720, and then we assessed apoptosis measuring activity levels of caspase-3 and -7. Vehicle-treated cells were used as controls. Consistent with its ability to increase PP2A activity and suppress cell growth, FTY720 showed a caspase-dependent proapoptotic effect, increasing caspase activity levels almost 7-fold in FTY720-treated RKO cells compared with vehicle-treated cells (Fig. 5A). In addition, caspase activity in FTY720-treated cells was markedly reduced when cells were pretreated with okadaic acid. These results were confirmed in the LoVo cell line (Fig. 5A).

Molecular effects of PP2A activation in colorectal cancer cells after FTY720 treatment

We next analyzed by Western blot analysis whether the FTY720 treatment had any effect in the phosphorylation status of previously described PP2A targets. Consistent with previous reports about the effects of
PP2A activation in other tumor models (27), FTY720 treatment decreased phosphorylation (activity) of the PP2A targets AKT and ERK1/2 without affecting their expression levels (Fig. 5B). Moreover, okadaic acid treatment rescued AKT and ERK1/2 phosphorylation in FTY720-treated RKO cells. Similar results were observed in LoVo (Fig. 5B), HT-29, and SW480 cells (Supplementary Fig. S11). Analysis in the HT-29 cell line showed decreased phosphorylation only for ERK1/2 (Supplementary Fig. S11). Moreover, we observed that phosphorylation on tyrosine 307 of PP2Ac was not affected in cells treated with FTY720 compared with cells treated with vehicle (DMSO; Supplementary Fig. S11). Altogether, these results would indicate that the molecular mechanism of action of FTY720 involves the inhibition of AKT and ERK1/2 signaling.

Figure 4. Colony-forming ability of untreated, FTY720-treated, and FTY720/okadaic acid (OA)-treated RKO and LoVo cells. Colony-forming assay showing effects of FTY720 alone or in combination with okadaic acid in RKO and LoVo cells.

Figure 5. FTY720 induces caspase-dependent apoptosis together with changes in the phosphorylation status of PP2A targets. A, caspase-3/7 assays in RKO and LoVo cells untreated (DMSO), and FTY720-treated alone or in combination with okadaic acid (OA). B, Western blot analysis showing AKT and ERK1/2 phosphorylation and expression after FTY720 treatment in RKO and LoVo cells.
We next analyzed PP2A, CIP2A, and SET levels after treatment with FTY720 alone or in combination with okadaic acid in RKO and LoVo cell lines. Interestingly, Western blot analysis showed that CIP2A decreased after FTY720 treatment and CIP2A levels were restored when cells where treated with FTY720 in combination with okadaic acid. No changes were observed in SET or PP2A expression. As expected, c-MYC levels decreased in correlation with CIP2A (Supplementary Fig. S12).

Altogether, these results would describe a novel mechanism of action of FTY720 through CIP2A and c-MYC deregulation.

**FTY720 potentiates antitumor activity of 5-fluorouracil, SN-38, and oxaliplatin in colorectal cancer cells**

To assess the effect of a combination between standard induction chemotherapy drugs used in colorectal cancer and FTY720, we treated colorectal cancer cells with either 5-FU, SN-38, or LOHP, alone or in combination with FTY720. Of importance, we observed that FTY720 enhanced the antitumor effects mediated by 5-FU (Fig. 6A), SN-38 (Fig. 6B), and LOHP (Fig. 6C) treatments in the RKO and LoVo cell lines. These data were also confirmed in DLD-1 (Supplementary Fig. S13) and HT-29 cells (Supplementary Fig. S14). Therefore, these results showed that FTY720 treatment has an additive antitumor effect when combined with either 5-FU, SN-38, or LOHP in colorectal cancer cells.

**FTY720 shows therapeutic effects in human colorectal cancer ex vivo models**

To further investigate the potential therapeutic effects of FTY720 in colorectal cancer and assess cytotoxicity of this drug in normal colon cells, we performed human colorectal cancer ex vivo models using five primary colorectal cancer tumors that were obtained from surgical specimens of patients newly diagnosed for adenocarcinoma. IHC analysis comparing samples of normal colonic mucosa and colorectal cancer from the same patient...
showed that FTY720 treatment induces an increased apoptosis (cleaved caspase-3) together with decreased proliferation (Ki-67) in tumor samples, whereas no significant changes were observed in control samples (Supplementary Fig. S15). These observations would support the observations made in vitro and indicate that cytotoxic effects of FTY720 are markedly reduced in normal colon cells.

Discussion

PP2A is a human tumor suppressor that regulates the activity of several signaling proteins critical for malignant cell behavior. We report here that PP2A is frequently inactivated in colorectal cancer cell lines and patient samples. In addition, we demonstrate that FTY720-induced PP2A activation leads to cell growth inhibition, impaired clonogenic potential, caspase-dependent apoptosis, and changes in the activation status of downstream targets such as AKT and ERK1/2. Importantly, FTY720 treatment shows an additive effect with the chemotherapy reagents 5-FU, SN-38, and LOH-P, suggesting that treatment with PP2A activators could be a novel therapeutic option in colorectal cancer in combination with standard chemotherapy.

To evaluate the importance of PP2A deregulation in colorectal cancer, we quantified PP2A activity levels in 21 patients with colorectal cancer (paired normal mucosa and tumor samples), observing a reduced PP2A activity in 19 out of 21 colorectal cancer patient samples (Fig. 1 and Supplementary Fig. S2 and Supplementary Table S2). PP2A assays were carried out with two different antibodies against PP2A (1D6 and FL-309) that showed similar results in all cases except in P4 (PP2A inhibition only with FL-309). Although the FL-309 antibody recognizes the full-length PP2A, the 1D6 antibody has been reported to preferentially recognize the demethylated fraction of PP2A (21–22), and this could be an explanation for the discrepancy observed in this case P4 between the PP2A inhibition affecting any of these PP2A subunits. In fact, the cancerous cell shows a wide variety of molecular strategies to inhibit PP2A, including hyperphosphorylation or downregulation of its catalytic subunit, mutations to inactivate PP2A in cancer cells (4, 9). Thus, we analyzed PPP2R2A and PPP2R5E, two regulatory PP2A subunits recently implicated in cancer (28–29) observing down-regulation of these subunits in, respectively, nine and three out of the 21 colorectal cancer cases (Supplementary Table S2 and Supplementary Fig. S5). These alterations could contribute to explain some of the differences observed in the PP2A activity levels of the patients with colorectal cancer. However, PP2A constitutes a large family of serine/threonine phosphatases, and in this work, we have only tested some of the potential mechanisms to inhibit PP2A. Although the catalytic and the scaffold subunits have two different variants, four unrelated families of PP2A regulatory subunits have been identified, including at least 26 different alternative transcripts and splice forms (5). Thus, PP2A has the ability to form a high number of different complexes with an also high number of potential alterations that could contribute to PP2A inhibition affecting any of these PP2A subunits.

To assess the potential therapeutic value of PP2A activation, we used FTY720 to treat colorectal cancer cells. FTY720 is an immunosuppressor and U.S. Food and Drug Administration (FDA)-approved drug for multiple sclerosis treatment. Interestingly, FTY720 has shown antitumor properties in several cancers. We considered this drug to treat colorectal cancer because together with its FDA approval, Nagaoka and colleagues studied the effect of FTY720 phosphorylation in breast and colon cancer, observing an anticancer activity against two colorectal cancer cell lines (HCT-116 and SW620; ref. 31). In addition, the pharmacologic activation of PP2A using...
FTY720 has been proposed as a therapeutic alternative for future treatments in patients with some leukemias (27, 32). Interestingly, it has been recently reported that FTY720 targets SET and then mediates tumor suppression via PP2A activation in lung cancer (33). Our results show that PP2A inhibition plays an important role in colorectal cancer transformation because the pharmacologic activation of PP2A in vitro and ex vivo using FTY720 reverses some of the malignant features of the colorectal cancer cells, whereas cytotoxic effects seem to be markedly impaired in normal colon cells (Figs. 3–5 and Supplementary Fig. S15). Moreover, we observed that the molecular mechanism by which FTY720 is acting involves the inhibition of the AKT and ERK1/2 (Fig. 5B), both PP2A targets, suggesting that this effect occurs via PP2A activation. In fact, we showed PP2A activation after FTY720 treatment but, unexpectedly, we did not observe any change in the PP2A phosphorylation levels (Supplementary Fig. S11), indicating that FTY720 activates PP2A by a mechanism alternative to the tyrosine-307 dephosphorylation. Interestingly, we observed that FTY720 led to decreased CIP2A levels (Supplementary Fig. S12), which indicates that in addition to its recently reported blockade of SET (33), FTY720 could be acting decreasing CIP2A expression. Indeed, these two events are in concordance with the PP2A activation observed after the FTY720 treatment because SET and CIP2A are two endogenous PP2A inhibitors. Furthermore, our results also showed that FTY720 exhibits additive antitumor effects with reagents used in standard chemotherapy such as 5-FU, SN-38 (active metabolite of irinotecan), and LOHP (Fig. 6), suggesting that FTY720 is a good candidate for future trials in combination with standard chemotherapy reagents in patients with colorectal cancer.

In conclusion, we report that functional inactivation of PP2A is a common event in colorectal cancer. In addition, we show that functional loss of PP2A activity occurs through contributing mechanisms such as overexpression of the PP2A endogenous inhibitors, SET and CIP2A, and downregulation of the regulatory PP2A subunits, PPP2R2A and PPP2R5E. Moreover, the potent antitumor effects observed after restoration of PP2A activity with FTY720 indicates that PP2A inhibition is an alteration with high relevance in colorectal cancer pathogenesis. Finally, the fact that FTY720 treatment has shown an additive effect to chemotherapy drugs highlights PP2A as a molecular target with a potential value in therapies combined with PP2A activators in colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: I. Cristobal, C. Carames, O. Aguilera, J. Madoz-Gurpide, F. Rojo, J. Garcia-Foncillas


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R. Rincon, C. Carames, C. Senin, S. Zaza, F. Rojo

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